Population Modeling and Clinical Trial Simulation

Part 2: Evaluating PK/PD and Outcomes Data and Generating Models for Clinical Trial Simulation Assessments

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Overview of Topics

Clinical Pharmacometrics and Trial Simulation

- **Important Aspects**
  - Asking the Right Questions
  - Modeling and Simulation Assumptions
- **Developing Models**
  - Modeling Variability
  - Generating Virtual Patients
    - [illegible]
  - Coping with Missing data
    - [illegible]
    - [illegible]
    - [illegible]
  - Modeling Time Course of Drug and Response
    - [illegible] Progress Models
    - [illegible] PK Outcome Models
    - [illegible] Liability Models
  - Modeling Trial Execution
  - Cost Function Models
    - [illegible] Right Complexity to Develop

Population Based Modeling and Clinical Trial Simulation

Clinical Trial Simulation and Population Modeling are Closely Related

- **Trial Simulation Used to Qualify Population Based Models**
  - Posterior Predictive Check - Simulate Data Using Model and Compare Simulated Data with Observed Data
- **Components of Population Models and Simulation Models are Similar**
  - Not All of the Models are Required
    - [illegible] Distribution Model Usually for Simulation, but Can Be Used [illegible] Missing Data During Modeling
- **Potential Uses of Both Must Be Defined and Specified Prior to Initiating Work**
  - Most Population Models Now Used for Simulation

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

General Issues

Model Development Must Be Complete

- Covariate Model Must Be Developed
- PK/PD Relationship Must Be Established and Confirmed
- Outcome Model Must Be Built
- Dose Regimen Options Must Be Reasonable and Consistent with Clinical Practice
- Analysis Plan Must Be Developed Prior to Initiation
- Sufficient Resources Must be Given to Modeling and Simulation

General Issues

How Should Drug Development Programs be Designed to Generate Sufficient Information About Adverse Events and Outcome?

- Dose and Schedule Dependence

Need for Surrogate Variables / Informative Covariates

- Genetics or Genomics Data
- Learning and Confirming

Need to Collect More and Better Information on Adverse Events and Response

- Atificial Intellegence and Fuzzy Logic Methods
- Collection of Patient Diary Information or Other Means

Selection of Desired Product Using Cost Functions

Response Surface Methods or Combinatorial Optimization

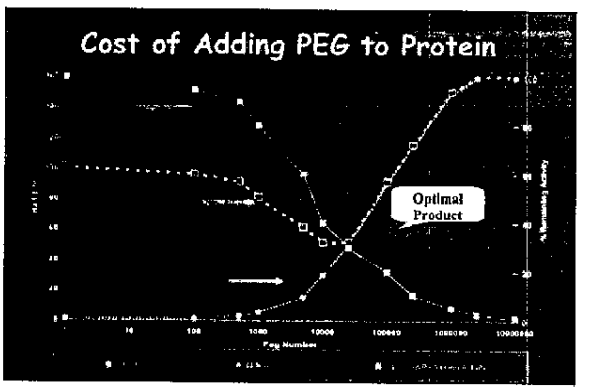
- Describe the Relationship Between Desired Product Performance and Costs
- Uses Objective Function To Select Optimal Solution

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Developing Reasonable Cost Functions

- Largely Empirical Functions
  - Function Describing Benefit of New Formulation
    - Expected Cost Savings Due to Lower Frequency of Hospitalization, Fewer Syringes
    - Convenience Factor (What Patients / Insurance Might be Willing to Pay)
  - Loss Function Based on Added Costs
    - Expected Increase in Desired Product Cost
    - Expected Increase in Development Costs
  - Constrain Search to Agents With Required Properties
    - e.g Hematopoietic Effects Must Wear Off in 20 Days
- Difficulty Because of Mixed Input
  - Most Commonly Work in Dollars as Continuous Function
  - Discrete Cut-Off Factors

Cost of Adding PEG to Protein



Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Basic Questions:

Basic Questions to Ask Prior to Beginning a Modeling or Simulation Analysis

- What Do You Need to Know?
  - The design of a simulation study is as critical as the design of a clinical protocol.
- How Well Do You Need to Know it?
  - Many models must be defined for simulation
  - Need to determine which ones must be "correct" and which ones can be "OK" but not perfect
- What Are the Consequences if You Are Wrong?
  - Hypothesis testing or sensitivity analysis must be conducted.
  - Models must be qualified

Model Based Assumptions

Outcomes are Dependent on Measure of Drug Exposure

- Dose, AUC, Cp_{ss}, Cp_{min}, Cp(t)
- Other Patient Factors Accounted For
  - Demographics
  - Prior treatment or Disease
  - Clinical Assessment of Disease Status

Relationship Between Exposure and Outcome Can Be Described

- Safety (Common), Efficacy (Rare)

Models are Predictive

- Model Can be Used to Extrapolate as well as Interpolate

Model is Qualified

Modeling Variability

Variability Models REQUIRED for Trial Simulation

- Necessary to Define Parameter Inter-Relationships
- Necessary for Predictive Performance

Population Based Models without Sufficient Variability Models Can be Problematic

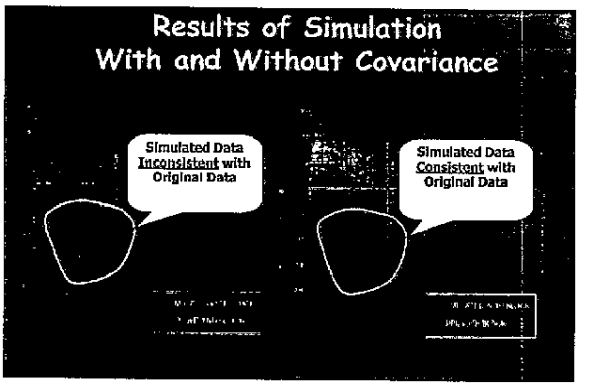
- Inter-Individual Variability
  - Covariance
- Inter-Occasion Variability
- Random Residual Variability

Variability is Critical in Any Simulation Analysis

- Patient Heterogeneity
  - Must maintain a vector of physiologically and medically reasonable covariates
- PK, PD, and Outcome Variability
  - Inadequate variance structure leads to simulated data that does not reflect original data

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Results of Simulation With and Without Covariance

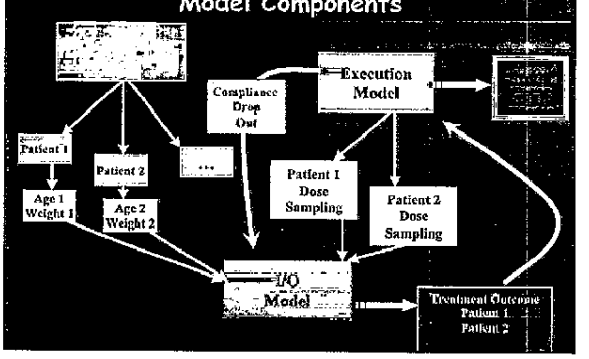


Population Based Modeling and Simulation Terminology

Need to Define Several Models

- Covariate Distribution Model
  - Defines the characteristics of the patients in the simulation experiment
    - Demographics
    - Concomitant disease or disease stage
- Input / Output Model
  - Defines the clinical indication and the drug that is being tested
    - Structural and Stochastic Models
      - PK, PD, Disease Progression, Outcomes
    - Covariate Models
      - Defines effect of covariates on PK, PD or Outcome Structural Models
- Execution Model
  - Everything Else!
    - Dosing Practice and Compliance
    - Drop out
    - Study Evaluation

Model Components



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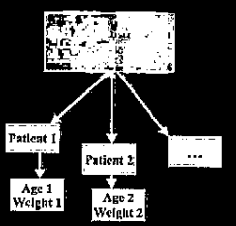
Covariate Distribution Models



Covariate Distribution Models

- Need to Generate Only Covariates That are Statistically and Clinically Significant
  - If No Covariate Models Identified, Covariate Distribution Models are Not Required
- Three Basic Approaches
  - Bootstrapping
    - Identification of Exchangeable Quantities
  - Assumed Covariate Distributions
  - Joint Functions of Covariate Distributions
    - Useful for Imputing Missing Data!

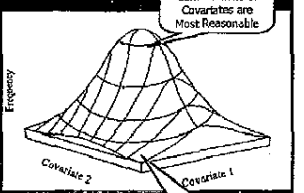
Developing Joint Functions

- Demographic and Patient Data Treated as Dependent Variables
- Demographic and Patient Data Fit to Functions
  - Relationships Between Demographic Data Developed
  - Covariance Structure Developed
- Random Residual Variability
  - Additive Model
  - Fixed to a reasonable and small value
    - I.e. Weight may have a fixed additive value of 0.5 kg

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Covariate Distribution Models Joint Function

- Joint Function Describes the Relationship of Patient Covariates (e.g. Age and CrCL)
- Establishes a Multivariate Density Function of These Covariates
- "Virtual Patients" Will have Reasonable Covariate Combinations



Other Methods for Dealing with Missing Data

Case Deletion

- Delete Patients With Missing Data
  - If demographic data, remove entire patient
  - If PK observations, delete missing data items
- Problem! If Many Patients Have Missing Data, Data Interpretation Can be Incorrect
  - Covariate or demographic model information may be lost
  - If many observations are below the limit of assay quantification, then modeling may be difficult
  - If patients dropped out, assessment of outcome is difficult

Other Methods for Dealing with Missing Data

Imputation

- Replace Missing Demographic Values With Median Value Determined From the Rest of the Data
  - Used for missing covariates - easy to do
  - Problem! Although this imputation will maintain the median value of the distribution, it alters the secondary characteristics of the distribution (e.g. variance)
- Replace Missing Observations Due to Assay Limits with ½ Lower Limit of Assay Quantitation
  - This is a fairly robust technique if data are relatively rich
- Fit the Data
  - Only useful if the number of missing observations is low (approximately less than 5% of the total number of observations)

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Other Methods of Dealing with Missing Data

Multiple Imputation

- Replace Missing Values with a Value Predicted Using Developed Function
  - For example, if you wish to impute missing PK data, use the PK model to simulate a value that is reasonable.
    - Error models MUST be implemented to provide variability
    - Must have a means of assuring that simulated data are reasonable.
  - If the PK data that are missing were all below the limit of assay quantitation, then any simulated values must be greater than 0 and less than the limit of detection.
- Fit the data
  - Used for missing Observations and missing covariates
  - Must create multiple data sets – usually 20 sets is sufficient
- Summarize Output
  - Mean parameter estimates for all data sets
  - Variance of the set of estimates
  - There are other statistics that are useful, please see a statistics text book for these

Dealing with Missing Data

Missing Data Do Not Always Have to be Restored

- If Covariates are Missing for a Subject, Covariate Identification is Difficult Unless Missing Data are "Restored"
- If many PK observations are not measurable due to assay limitations
  - May have problems identifying model parameters
- Analyzing Study Outcomes Where There is Drop-out
  - Last Observation Carried Forward Can Bias the Analysis. Imputing Data May be More Reasonable

Relative Utility of Methods

Case Deletion

- Easy to do but can alter data interpretation

Imputation

- Easy to do but limited utility and can alter data interpretation

Multiple Imputation

- Difficult to do but can be useful, particularly useful for non-measurable PK or PD values

Joint Function

- Somewhat difficult to do but most robust method for replacing missing data especially for covariates

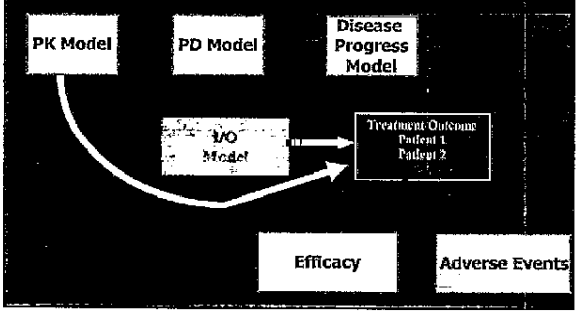
Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Developing Input/Output Models

Structural Models
- PK, PD, Disease Progression, Outcome
- Covariate Models
  - Defines effect of covariates on PK, PD, Disease Progression, Outcome

Methods of Development
- Fitting Data Obtained in Prior Studies or Trials Involving Related Drugs
- Literature Research
- Expert Input
- Assumption Based

Input / Output Models



PK/PD Models

Pharmacokinetic (dose, concentration, time)
- drug disposition in individuals & populations
- disease state effects (renal & hepatic dysfunction)
- intervention effects (hemodialysis)
- concurrent medication effects
- pharmacogenetic influences

Pharmacodynamic (dose or concentration, effect, time)
- physiologic & biomarkers
- surrogate endpoints
- clinical effects and endpoints

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Empirical and Mechanistic PK/PD Models

Role of Empirical PK/PD Models
- Sometimes Empirical Approach is the Only Option
- Specialized Applications
- Results May Guide Selection of Mechanistic Model
- Computationally Easier to Develop

Role of Mechanistic PK/PD Models
- Prior System Information Useful
- Knowledge Gained on Drug Effects has General Utility
- Extrapolation and Prediction of New Regimens or Formulations More Reliable
- Numerically Difficult to Develop and Parameter Identifiability Can be Problematic

Rational For Disease Progress Models

Accounting for Disease Progress is Important For the Analysis of Drug Effects
- Better Able to Discern True Effect
  - Curative
  - Palliative
  - Both?
- Improves Reliability of Simulation Work
  - Accounts for Placebo Response
  - Visualization of the time course of disease in treated and untreated conditions
- Developing New Drug Candidates
- Visualize the Drug Use Better
  - Evaluation of various disease intervention strategies

Convert Data into Understanding!

Disease Progression Model Definitions

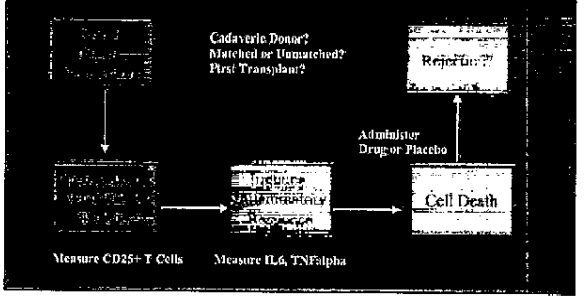
Quantitative model that accounts for the time course of disease , $S(t)$:
- "Symptoms" - measures of how a patient feels or functions *("clinical endpoints")*
- "Signs" - physiological or biological measurements of disease activity *("biomarkers")*
  - *"Biomarkers" (unvalidated markers associated with clinical outcome)*
  - *"Surrogate Endpoints"* (validated markers predictive of, or associated with Clinical Outcome)
  - *"Outcomes"* (measures of global disease status, such as pre-defined progression or death)

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Disease Progress Model Building Process

- Talk to a Disease Specialist
- Draw pictures of time course of disease
- Translate into disease progress model
- Explain the models/parameters
- Ask Disease Specialist for advice on factors influencing parameters
- Translate into models of parameters

Example Construction of a Disease Model



Data for Disease Progress Models

- Use Measured Concentrations and Observations
  - This is easy to do
- Use a "Link" model or Effect compartment) to Create Lag Between Observed Concentrations and Effects
  - This can be helpful as the time course for change in disease status is usually not the same as the time course of the drug
- Use Probability Models if no Continuous Measurement Available
  - Literature
  - Expert Input

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Issues Involving Building Disease Progress Models

Lack of Continuous Measurements for Building Disease Progress Model

- Literature Data
- Expert Input

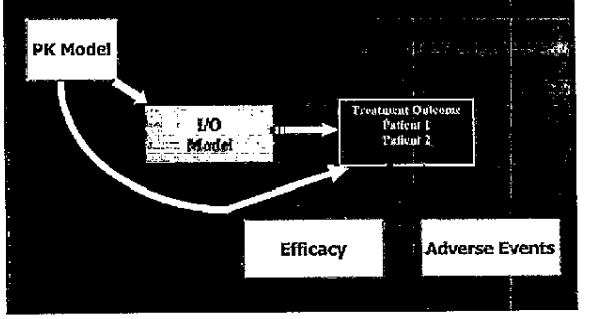
Resources

- Lack of Available Data for Untreated Patients
- Time Required to Collect Data and Develop Model
- Variability Inherent in Data May Require Large Numbers of Subjects to Determine Parameters Accurately

Role of Modeling Clinical Outcomes

- Improve Mechanistic Understanding
- Detect Factors Predictive of Inter- and Intra- Patient Variability for Both PK and Adverse Events
- Predict Consequence of Changing PK, PD and Dose Regimen
- Dose Schedule Optimization

Clinical Outcome Models



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Adverse Event Classification

Adverse Event Relationship to Test Drug

- Classifications:
  - Definitely, Probably, Possibly, Unlikely
- Grades
  - None, Mild, Minor, Moderate, Severe

Frequency and Immediacy of Adverse Event

- "A" Classification (Accountable, Predictable)
  - High Frequency, Immediate
  - High Frequency, Delayed
  - Low Frequency, Immediate
  - Low Frequency, Delayed
- "B" Classification (Bizarre, Unpredictable)
  - Idiosyncratic

Clinical Outcome Information

Measurement of Outcome

- Summary Observation of Event
  - Categorical or Ordinal Scale
- Measurements of Time Course of Events
  - Continuous Data

Frequency of Measurement

- Single Summary Description (e.g. Highest Grade)
- Protocol Defined Times for Collection
- Repeated Measurements as Event Occurs

Establishing PK/Outcome Relationship

Re-Challenge

- Links Summary Events to Drug Exposure

Temporal Correlation

- Links Time Course of Drug Exposure to Time Course of Adverse Event or Response

Sufficient Information Available to Elucidate Relationship

- PK/Outcome Relationship May Follow "Traditional PK/PD Relationship" or May be Dependent on a "Threshold" Value

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

PK/PD Relationships for Clinical Outcomes

	Summary PK variable	Full PK time-course
Summary Variable Of Outcome Event	Highest Grade Versus AUC	Highest Grade Versus Cp-t
Full Outcome Event Time Course	Outcome Time Course Versus AUC	Outcome Time Course Versus Cp-t

Why Use the Full PK Time Course to Describe Relationship?

The Most Relevant Feature of the Exposure Relating to Magnitude of Outcome Can be Estimated.

- Effect May be Due to Peak Concentration, AUC, Time Course But using Full PK data Confirms These Theories
- May Better Establish Causality of Adverse Event or Response

Covariate Associations with Probability of Clinical Outcome May be Attributed to the Appropriate Parameter Variability

- Disease Status effect on Clearance?

OR

- Disease Status effect on Outcome?

Why Use the Full PK Time Course to Describe Relationship?

Dose, AUC and Threshold Models are Special Cases

- Most Appropriate Measure of Exposure is Usually Time Course of Exposure
- Full Time Course Describes Increases and Decreases and to Maximum Concentration and Response

(Slightly) More Mechanistic to Use Data From the Full Time Course

- PK
- PK and Outcome

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Why Use the Full Time Course of The Clinical Outcome Information?

- Maintain All Information.
- More Than a Single Aspect of the Outcome May be Important.
  - Time Course of Outcome May be Correlated with Concentration
- Individuals with Different Quantity/Quality of Data Can be Pooled.
  - Population Based Approach

Why Use Summary Variables to Describe Clinical Outcom?

- Summary Variables Perceived to Capture the Most Important Aspect of the Adverse Event or Efficacy
  - May Discard Important Information (e.g. Time Course)
- Ease of Analysis
  - But... "No Pain No Gain" (Results of Analysis Have Less Utility)
- Often Censoring in Adverse Event or Efficacy Data
  - Dropouts May Reflect High Grade Adverse Event or Failure to Respone
  - Informative Missingness

Use of Summary Variables for PK/Clinical Outcome Assessments

- Majority of Experience in Assessing Summary Variable Relationships.
  - Dose or AUC versus Grade of Outcome
  - Problem with Loss of Crucial Time Information
- Few Modeling Examples Have Proven Value in Dosing Schedule Optimization.
  - Cancer Chemotherapy
- Mechanistic Models are Complex
  - Physiology Often Poorly Understood
  - Technical Issues for Developing Models
    - Requirements Needed

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Timing of PK/Outcome Model Development

- Continuous PK and Continuous Outcome Data
  - PK/AE Models Can be Started in Early Phase of Development
- Continuous PK and Summary Outcome Data
  - Usually Require Large Numbers of Subjects to Avoid Bias
  - Often Need to Wait Until Phase II
  - Pooling Data Across Indications May be an Option
- Summary PK and Summary Event Data
  - Usually Require Large Numbers of Subjects to Avoid Bias
  - Often Need to Wait Until Phase II
  - Pooling Data Across Indications May be an Option

Integrating PK/Outcome Models into Drug Development

- Development of PK/Outcome Model is Frequently Conducted Retrospectively
  - Integrated PK/AE and PK/Efficacy Analysis Provides Opportunity to Test Model and Improve Drug Dose Regimen
  - Approximately 20% of Marketed Drugs Undergo Post-Marketing Dose Adjustment!
- Integrated Approach Lends Statistical and Scientific Validity to PK/Outcome Model Results
- Use of PK/Outcome Models Can Provide Better Assessment of Treatment Effects Than Traditional Statistical Assessments
  - Permutation or Randomization Test
  - Utility for Clinical Trial Simulation

Approaches for Analyzing Summary PK/Clinical Outcome Data

- Approach Dependent on Data Available and Project Needs
  - Continuous PK/Outcome Model
  - Categorical or Ordered Categorical Logistic Regression
    - Adverse Event or Efficacy Data as Available only as Grades
  - Hazard Models
    - Assessment of Risk of event or survival.
  - Time to Event Models
  - Count Models
    - Assessment of Frequency

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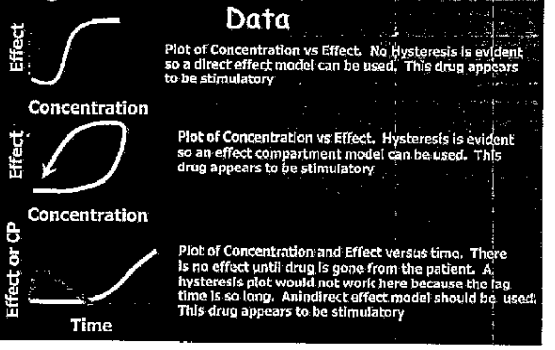
Development of Continuous PK/Outcome Models

Determine the Type of PD Model That Best Describes Response

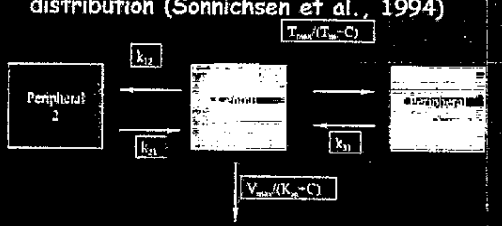
- Direct Effect
  - No Lag Time to Effect
  - Stimulatory or Inhibitory Effect?
  - Baseline Response?
- Effect Compartment
  - Short Lag Time due to Diffusion?
  - Stimulatory or Inhibitory Effect?
  - Baseline Response?
- Indirect Effect?
  - Longer Lag Time Due to Drug Effect Occurring Many Steps Prior to Event
  - Stimulatory or Inhibitory?

Diagnostic Plots for Continuous Event Data



Paclitaxel Pharmacokinetics

Non-linear elimination & non-linear distribution (Sonnichsen et al., 1994)



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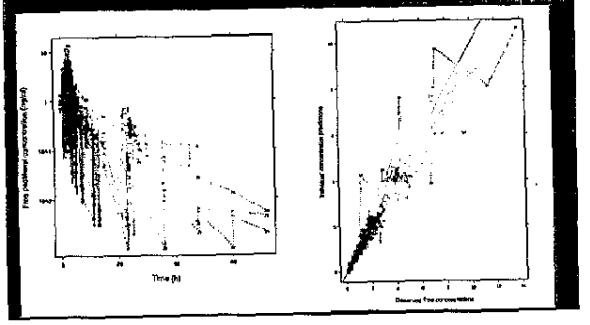
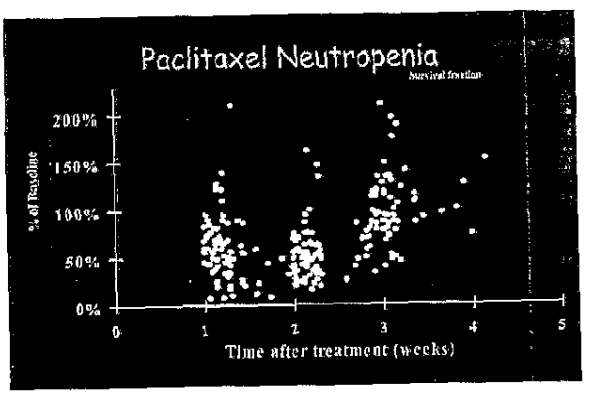
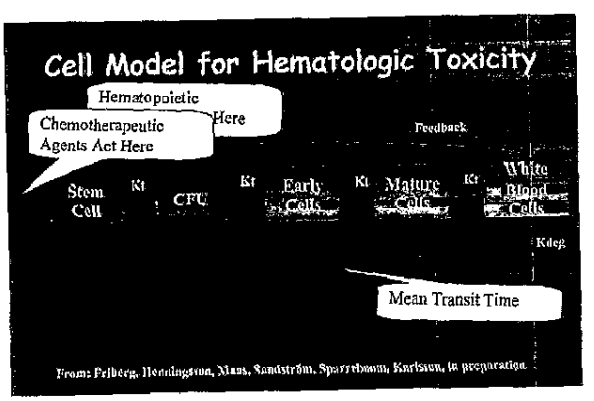
PK Model of Paclitaxel



Paclitaxel Neutropenia



Cell Model for Hematologic Toxicity



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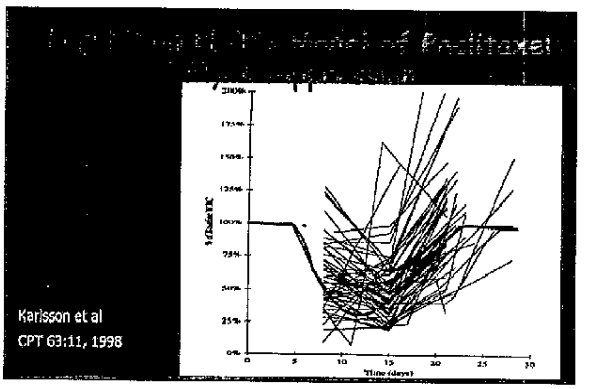

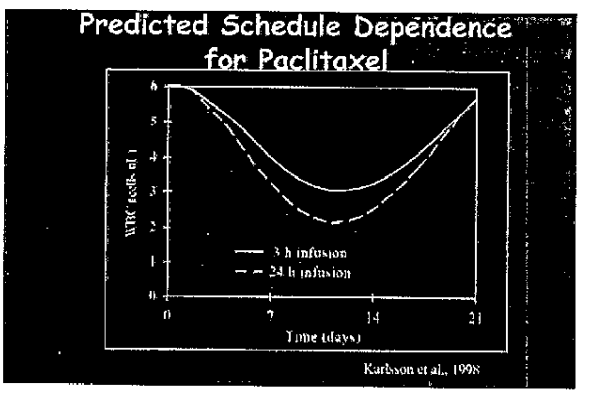

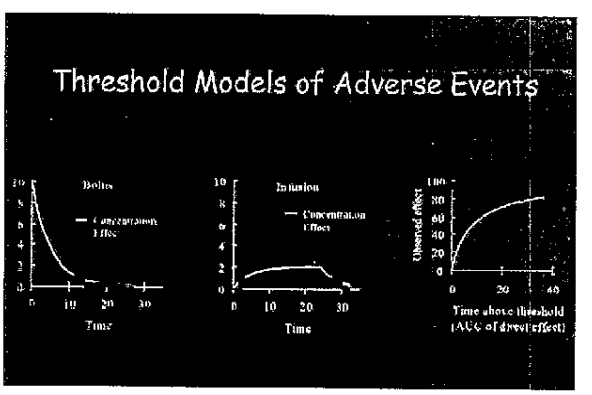

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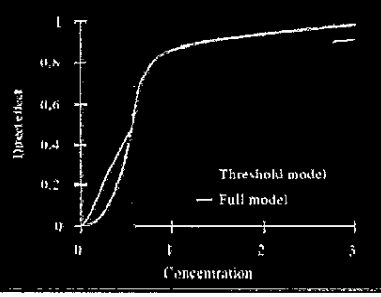
Comparison of Threshold Model with Full Model



Categorical Data

Measurement Scale is a Set of Categories

- Nominal (e.g. Success / Failure)
- Cardinal (e.g. Caucasian Asian Hispanic)
  - Non Ordered and Unrelated
- Ordinal (e.g. Mild Moderate Severe)
  - More Than 2 Response Levels
  - Response Levels are Related and Ordered
  - More Than One Observation Per Patient

Usually Considered Qualitative But May be Treated as Quantitative

- m Levels and (m-1) Indicator Variables
  - Levels Used as Actual Values

Logit Models for Categorical Data

Analysis of Ordered Categorical Response is Usually Referred to as "Logistic Regression"

For a Probability (π) Between 0 and 1

- Logit Model : $g(\pi) = \log [\pi / (1-\pi)]$
  $= \alpha + \beta$
- Maps the Probability onto a + Infinity to - Infinity scale
- Solving for the Probability:

$\pi(X) = \exp(\alpha + \beta X) / (1 + \exp(\alpha + \beta X))$

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Building Logit Models

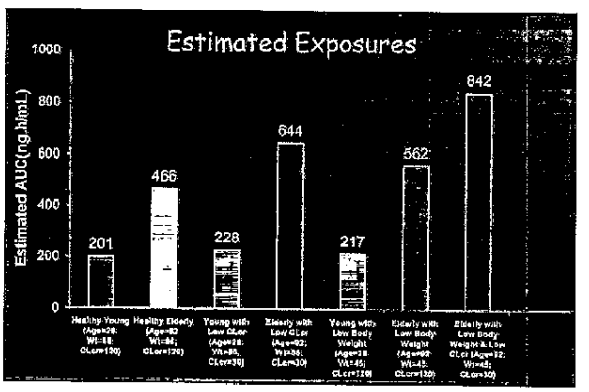
Frequency Trends Must be Established
- Plot of Adverse Event Frequency by Grade and Treatment

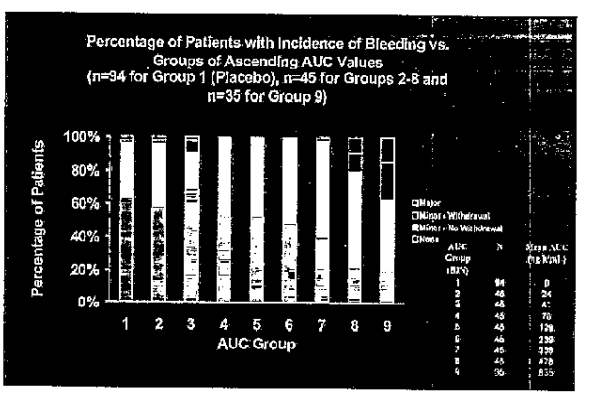
Models Sensitive to Initial Estimates
- Transform Raw Data to Logit Plots
- Use Estimates from Graphic Evaluation

Generate Data Base of Summary PK Data and Adverse Events
- Can Do Simultaneous Continuous / Odd Type Fit if Desired

Fit Data Using Laplacian with Likelihood Option

Testing:
- Plot of Raw Data versus Predicted Probability of Response
- Bootstrap to qualify model

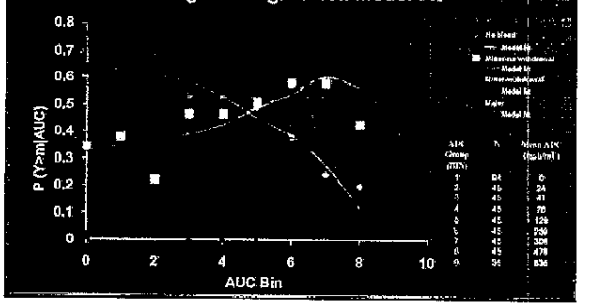




Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Logit Emax Model

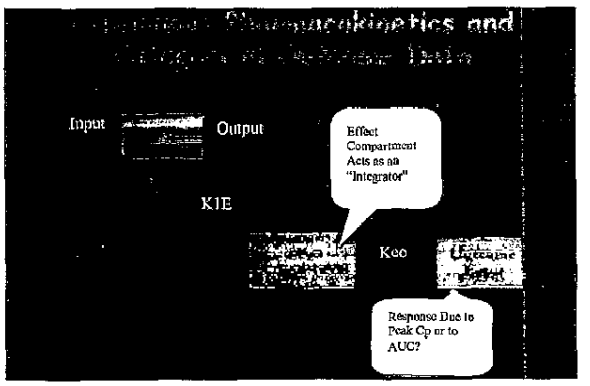
Individual Probabilities Calculated from the Raw Data versus Exposure (AUC) with Logistic Regression Model Fit



Fit of Pharmacokinetics and Categorical Clinical Outcome Data

- Develop Model Describing Time Course of Pharmacokinetics
- Correlate Pharmacokinetics to Outcome by Link Model
  - Effect Compartment Provides a Way to Estimate "Lag Time" Between Drug Administration and Onset of Event
- Estimated Value of Keo Yields Information About Importance of Different Measures of Exposure as Predictors of Adverse Events or Efficacy
  - Short Keo Suggests Peak Concentrations May be More Predictive
  - Long Keo Suggests AUC May be More Predictive

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001



Continuous Pharmacokinetics and Categorical Clinical Outcome Data

Options To Handle Data

- Simultaneous Fit of Continuous and Categorical Summary Data
- Serial Fit of Continuous and Categorical Summary Data
- Investigate Various Summary Parameters for PK for Predictive Ability
  - Css, AUC, Cmax

Selection of Analytical Approach Depends on Needs of Development Project and on Available Data

Hazard Functions

Hazard Functions Define the Rate of Occurrence of An Event

- Instantaneous Progression
- Hazard Can Be Defined Using Several Functions
  - Constant
  - Linear
  - Exponential
  - Other (*i.e.*, Weibull)

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Hazard Functions

Cumulative Hazard is the Integral of the Hazard Over a Pre-Defined Period of Time

- Describes the Risk
- Translates or Correlates Pharmacodynamic Response into a Useful Measure of Outcome
  - Assessment of Likely Benefit or Adverse Event Comparison With Existing Therapy

Hazard Functions

Define "T" as Time To Specified Event (Fever, Infection, Sepsis)

- T is a Non-Negative Random Variable from Homogeneous Population
- T is Continuous (*i.e.*, time)
- T is Characterized by:
  - Hazard: Rate of Occurrence of Event
  - Cumulative Hazard or Risk
  - Survival: Probability of Event NOT Occurring Before Time = t

Hazard Models

Hazard is Assumed to be a Continuous Random Variable

- Can be Function of Biomarkers (e.g. Neutrophil Count or other markers)

Hazard Functions can be Adapted for any Clinical Endpoints Evaluated at Fixed Time Points (e.g. During Treatment or On Protocol)

- Efficacy
- Adverse Events

Source: https://www.industrydocuments.ucsf.edu/docs/rrjk0001

Survival Function

S(t) = P(T > t)

Monotone, Decreasing Function

Survival is 1 at Time=0 and 0 as Time Approaches Infinity.

The Rate of Decline Varies According to Risk of Experiencing an Event

Survival is Defined as

$$S(t) = \exp(-H(t))$$

Using Hazard Functions in PK/PD Models

If Hazard Function is Defined as a Constant Rate "K" Such that

$$h(t) = K$$

Then the Cumulative Hazard is

$$H(t) = \int_0^t K dt = Kt$$

$$Kt = -\ln[S(t)]$$

Survival is

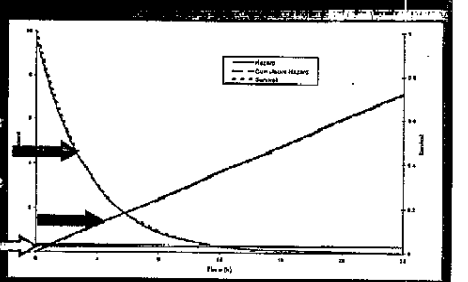
$$S(t) = \exp[-Kt]$$

Hazard, Cumulative Hazard, and Survival

In This Example Hazard Remains Constant

Cumulative Hazard Increases With Time

Survival Drops



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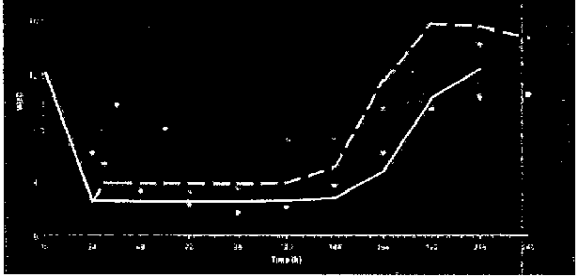
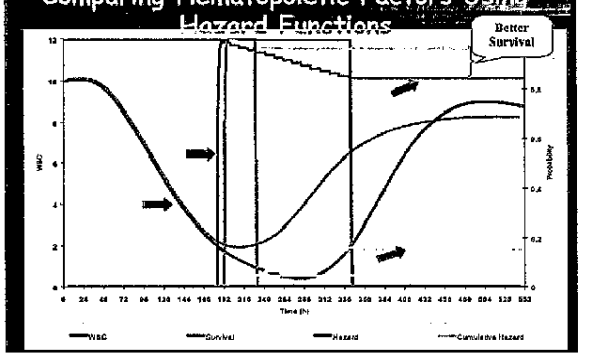
Example: Comparing Neutropenia With Different Hematopoietic Factors



Comparing Neutropenia with Different Hematopoietic Factors

- New Product Reduces Nadir and Recovery Time
  - Is the Improvement Enough to See Clinical Benefit?
- Evaluation of New Product More Relevant if PK and PD Changes Related to Clinical Outcome
  - Hazard Functions

Comparing Hematopoietic Factors Using Hazard Functions



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